REMARKS

Claims 1-6, 10-13, 23, 28-30, 40-42 and 75-86 are pending in the instant application. Claims 1-5, 23, 28-30, 40-42, 75 and 76 are withdrawn for being directed to a non-elected invention. Claims 6, 10-13 and 77-86 stand rejected. No amendments are made at this time.

As a preliminary matter, the response can be properly entered after final as no claim amendments are made, therefore no further search or consideration is required. Moreover, the rejection in the outstanding Office Action was made based on a newly cited reference published in 1998. Therefore, Applicant could not have responded to the rejection previously. Consideration and entry of the remarks herein is respectfully requested.

Election/ Restrictions

Applicant acknowledges the restriction of the claims in the instant application. Applicant requests consideration of rejoinder upon indication of allowable matter in the application.

Withdrawal of Rejections of Claims under 35 U.S.C. §112 and §103

Applicant thanks the Examiner for the withdrawal of the rejection of claims for alleged lack of enablement.

Applicant also thanks the Examiner for withdrawal of the rejection of claims 6, 10-13, and 77-81 for allegedly being unpatentable over Schouten et al (2002) in view of Maire et al. (2002) and Lecomte (2002), and the rejection of claims 82 and 83 for allegedly being unpatentable over Schouten et al (2002) in view of Maire et al. (2002), Lecomte (2002) and Nazarenko.

Rejections of Claims under 35 U.S.C. §103

The Office Action has newly rejected claims 6, 11-13, 77-81 and 84-86 under 35 U.S.C. §103 for allegedly being unpatentable Schouten et al (2002), as cited on the IDS of 08/25/2006, in view of Watanabe et al (1998).

The Office Action has further newly rejected claims 82 and 83 under 35 U.S.C. 103(a) for allegedly being unpatentable over Schouten et al (2002) in view of Watanabe, further in view of Nazarenko et al (2002).

For the sake of brevity, the rejections will be addressed simultaneously. The rejection fails because the references, even when combined, fail to teach the instantly claimed invention. Moreover, there is no suggestion to combine the teachings of Watanabe and Schouten for at least the following reasons.

The Office Action asserts that Schouten teaches the detection method instantly claimed. Applicant respectfully disagrees that the method provided by Schouten is the same as the method that is claimed. However, as the Office Action notes, Schouten provides no teachings in regard to analysis of a G35A KRAS mutation.

The deficiency of the teachings of Schouten are alleged to be overcome by Watanabe. The Office Action asserts that Watanabe teaches the analysis of the G35A mutations of the KRAS2 gene and that the quantitated level of the KRAS2 G35A mutation is indicative of pancreatic cancer as opposed to chronic pancreatitis.

Applicant submits that Watanabe teaches that although K-ras mutations were associated with pancreatic cancer, the usefulness of the marker in diagnosis was questionable at best. In the abstract, Watanabe teaches:

> K-ras mutations at codon 12 (KRM) have been detected in approximately 80% of samples of pure pancreatic juice (PPJ) from patients with pancreatic cancer (PCa) and are a promising potential tumor marker. ***However, the frequent presence of KRM was reported in PPJ from noncancerous patients as determined by a highly***

> ***sensitive method, raising questions as to the cancer specificity of this marker***.... When 11,020 RLUs was taken as the cut-off value, KRM was detected by PCR-HPA in 19 (66%) of 29 of PCa and one (4%) of 26 of CP cases. Analysis of PPJ by PCR-RFLP demonstrated KRM in 22 (79%) of 28 of PCa and five (19%) of 26 of CP cases. ***However, four of five patients with CP who were KRM-positive by PCR-RFLP were defined as negative by PCR-HPA, suggesting that PCR-HPA is superior to PCR-RFLP for the discrimination between PCa and CP.***

The paragraph bridging pages 341-342 of Watanabe teaches the failings of other methods to differentiate between chronic pancreatitis and pancreatic cancer.

> Polymerase chain reaction (PCR) and allele-specific oligonucleotide (ASO)-dot blot hybridization (DBH) identified KRM [K-ras mutation] in the PPJ [pure pancreatic juice] of 11 (55%) of 20 patients with PCa [pancreatic cancer] (10).

suggesting that the methods were not sufficiently sensitive.

In the first paragraph of the Discussion (page 345), Watanabe discusses other methods that were oversensitive that provided similarly inaccurate and inconsistent results. Specifically, Watanabe states:

> Recently, Yanagisawa et al. (16) and Caldas et al. (17) reported that 10 (63%) of 16 and five (71%) of seven selectively microdissected specimens of benign mucous cell hyperplasia of pancreatic ductal epithelium with chronic inflammation had KRM, respectively..... Tada et al. (18) reported detection of KRM in 57 and 42% of PPJ samples in 7 CP [chronic pancreatitis] and 12 healthy cases, respectively, using the highly sensitive and specific PCR method described in their previous report (12).

Further, the results from the two methods used by Watanabe did not agree.

> The incidence of KRM was determined as 19 (66%) of 29 patients by PCR-HPA, and 22 (79%) of 28 by PCR-RFLP.... five cases were found to be positive by PCR-RFLP and negative by PCR-HPA, whereas the remaining case (patient 24) was negative by PCR-HPA.

Therefore, one of skill in the art would understand that methods to differentiate chronic pancreatitis from pancreatic cancer based on the presence or absence of K-*ras* mutations typically fail.

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) ***Watanabe clearly teaches that the art of differentiation between chronic pancreatitis and pancreatic cancer is unpredictable, if not nearly impossible.*** Although one method was found to be predictive, the teachings that all other methods, including other PCR based methods, provided unsatisfactory results cannot be ignored.

The Court has addressed the issue of obviousness in chemical cases since the decision of *KSR*. Specifically the court stated:

> While the KSR Court rejected a rigid application of the... TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying '***a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does***' in an obviousness determination.
>
> When there is a design need or market pressure to solve a problem and there is a finite number of identified, ***predictable solutions***, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. *Takeda Chemical Industries Ltd. v. Alphapharm Pty.* 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The Federal Circuit in applying *KSR* noted that the TSM test need not be strictly applied, but that a finite number of ***predictable solutions*** must be available. Applicant submits that no such solutions were available in the art at the time of filing.

Section 2144 of the MPEP sets forth potential rationales for combining references.

> >II. < THE EXPECTATION OF SOME ADVANTAGE IS THE STRONGEST RATIONALE FOR COMBINING REFERENCES
>
> The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from ***a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination***. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). >See also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick, 464 F.3d 1356, 1368, 80 USPQ2d 1641, 1651 (Fed. Cir. 2006) (emphasis added).

Given that ***Watanabe provides one method out of many tested that provides results that correlate with actual diagnosis***, no convincing line of reasoning based on scientific principles can be made that the combination of references would provide some advantage over the teachings of Watanabe, or even success. Further, Watanabe teaches that the PCR-HPA method is quick and easy to perform. Watanabe states that method

> can be easily carried out within 30 min, because ***it is unnecessary to separate the hybridized from the non-hybridized acridinium-ester-labeled DNA***. (page 346, first full paragraph, emphasis added)

The method of Schouten requires that the probe ligation products be separated by gel electrophoresis (see, e.g., Figure 2). Not requiring such a step is stated to be an advantage of the method of Watanabe. Although Watanabe is relied on to provide support for the claim limitations related to mutations in K-*ras*, references must be taken ***as a whole***, including teachings that teach away from the combination of the references. Schouten requires a step that is taught by Watanabe to be unnecessary

and time consuming. There can be no motivation to modify Watanabe to include such a step.

Further, even Schouten teaches a preference for methods which are less time consuming (first page, middle of second column). Therefore, one of skill in the art would use the detection method of Watanabe, not Schouten.

The Office Action asserts that the detection of a particular mutation level is merely a matter of choice. However, Watanabe teaches that "the minimal level of detection for each DNA probe was 5% of the K-*ras* mutants in template DNA... plasmid or with cancer cell lines." The instantly claimed invention requires the detection of a mutation frequency of 0.6% (claim 11). The desire to have a better detection limit does not make modifications of the assay to improve the detection limits trivial.

The assertion of the Office Action that the method of Schouten is the same as the instantly claimed method, with which the Applicant disagrees, is said to be capable of detecting mutation levels of 10%, 1%, and 0.1%. There is no teaching or suggestion in Schouten that the method of Schouten would provide the claimed level of detection. An obviousness rejection cannot rely on alleged inherent and unrecognized properties of the cited art. An obviousness rejection must be made by considering what the references would have taught one of skill in the art ***at the time of filing of the application***.

On page 8 of 13, first column, Schouten et al. teaches that

> The excellent reproducibility of relative signals obtained ***enabled the detection of a single extra copy of a probe target sequence per diploid genome***. (emphasis added)

That is, ***a 50% increase*** in copy number could surprisingly be detected. Based on statements within Schouten, it would not have been obvious to one of skill in the art to try to use the method of Schouten to detect small changes in a portion (e.g., 10%, 1%, 0.6%, 0.1%) of the target present as are possible with the method of Watanabe.

The method of Schoten designed predominantly to detect large deletions (1N) or additions (3N) in genomic DNA, where the normal copy number is 2N (see e.g., the abstract). This is accomplished by ligating oligonucleotides to different regions of the genome, PCR amplifying them using tailed fluorescently labeled primers, and measuring the relative concentration of amplicons using capillary or gel electrophoresis. It can be used to detect 3 copies of chromosome 21 (Down's syndrome) or the X chromosome, whole exon deletions of BRCA2, exon losses of the mismatch repair gene hMLH1 and hMSH2, loss of the tumor suppressor gene p16/cdkn2b, extra copies (amplification) of erbb2, and germline mutation of the cystic fibrosis gene, cftr.

Detection in gains and losses in chromosomal regions refer to ***increases of 1.5-6.5 fold*** (page 9 of 13, second column-page 10 of 13, first column). A point mutation is detected in a heterozygote carrying a CFTR mutation that causes cystic fibrosis. The results from the assay are shown in Figure 8. The inequality in the size of the wild-type and F508 mutant peaks, when the sequences would be expected to be present in identical amounts, would suggest to one of skill in the art a limit on the accuracy of the determination of relative quantities of nucleic acid sequences.

In the Discussion section, possible applications are considered by Schouten (see page 12 of 13, second column). ***All of the applications consider fold changes in the amount of a particular sequence present***. Based on the teachings of Schouten, one could not expect that mutations present in 10%, 1%, 0.6%, or 0.1% of the templates in the sample could be detected using the method provided therein.

Nazarenko cannot make up for the deficiency of the combination of the Schouten and Watanabe and the rejection fails for the reasons set forth above. Nazarenko is relied upon to teach multiplex PCR using multiple fluorogenic primers (see abstract). However, Schouten teaches against the use of fluorescent primers. Specifically Schouten states:

> [R]eal-time PCR provides the possibility to detect several fold amplification of chromosomal sequences; however, its use in a multiplex assay is severely limited by spectral overlap of the fluorescent dyes used. In addition, the

> presence of multiple primer pairs in multiplex reactions reduces the robustness of PCRs and reliability of the quantification.

Therefore, one of skill in the art would not be motivated to modify Schouten to perform fluorescent multiplex assays as Schouten teaches against them. Therefore the references cannot properly be combined.

Withdrawal of the rejections is respectfully requested.

CONCLUSIONS

Applicant believes the pending application is in condition for immediate allowance. However, if the Examiner believes that there are any outstanding issues in the case that could be addressed by telephone conference, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss the matter.

PETITION AND FEE AUTHORIZATION

It is believed that there is no fee due with this response. However, if a fee is due, the Commissioner is authorized to charge any fees associated with this submission, or any other submission by this Firm in relation to the instant application, to our Deposit Account, No. 04-1105, Reference 62310(71699). Any overpayment should be credited to said Deposit Account.

Dated: August 23, 2010

Respectfully submitted,

Electronic signature: /Colleen McKiernan/
Colleen McKiernan, Ph.D..
Registration No.: 48,570
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5555
Attorneys/Agents For Applicant